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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 221/10, 209/62, A61K 31/435, 31/40, C07D 491/04 // (C07D 491/04, 317:00, 221:00)

A1

(11) International Publication Number: **WO 98/30546**

(43) International Publication Date: 16 July 1998 (16.07.98)

(21) International Application Number: PCT/EP98/00043

(22) International Filing Date: 7 January 1998 (07.01.98)

(30) Priority Data:
97100172.2 8 January 1997 (08.01.97) EP
(34) Countries for which the regional or international application was filed: CH et al.

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: TRICYCLIC BENZO[e]ISOINDOLES AND BENZO[h]ISOQUINOLINES

(57) Abstract

The present invention is concerned with novel benzo[e]–isoindoles and benzo[h]isoquinolines. Since the compounds in accordance with the invention can bind to serotonin receptors ($5HT_2$), they are especially suitable for the treatment or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive–compulsive disorders, social phobias or panic attacks, mental organic disorders, mental disorders in childhood, aggressivity, age–related memory disorders and behavioural disorders, addiction, obesity, bulimia, etc., nervous system damage caused by trauma, stroke, neurodegenerative diseases, etc.; cardiovascular disorders such as hypertension, thrombosis, stroke, etc; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

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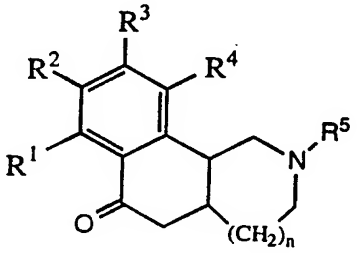
Tricyclic benzo[e]isoindoles and benzo[h]isoquinolines

The present invention relates to tricyclic compounds. In particular, it relates to benzo[e]isoindoles and benzo[h]-isoquinolines of the general formula



I

wherein

R^1-R^4 each independently signify hydrogen, halogen, hydroxy, lower alkyl, lower-alkoxy or phenyl or R^2 and R^3 together represent -O-CH_2-O-;

R^5 signifies hydrogen, lower-alkyl or benzyl; and

n signifies 0 or 1

as well as pharmaceutically acceptable acid addition salts of the compounds of formula I, with the exception of racemic 2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one.

The compounds of formula I are novel with the exception of rac. 2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one (DE 19 26 022). The compounds described in this Offenlegungsschrift have antiphologistic properties for use against inflammations as well as oedemas following contusions, distortions or fractures.

Since the compounds in accordance with the invention can bind to serotonin receptors ($5HT_2$), they are especially suitable for the treatment or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive-compulsive disorders,

social phobias or panic attacks, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc., nervous system damage caused by trauma, stroke, neuro-degenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

Objects of the present invention are compounds of formula I and pharmaceutically acceptable acid addition salts, their racemic mixtures and the corresponding enantiomers thereof per se and as pharmaceutically active substances, the manufacture of these compounds and salts, medicaments containing a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, the production of such medicaments and the use of the compounds of formula I and their pharmaceutically acceptable salts in the control or prevention of illnesses, especially of illnesses and disorders of the aforementioned kind, and, respectively, for the production of corresponding medicaments. Only the named known compound itself is excluded from the objects of the present invention as previously defined.

The term "lower" denotes residues with a maximum of 7, preferably up to 4, carbon atoms; "alkyl" denotes straight-chain or branched saturated hydrocarbon residues such as methyl, ethyl, propyl, isopropyl, n-butyl, 2-butyl or t-butyl and "alkoxy" denotes an alkyl group bonded via an oxygen atom, such as methoxy, ethoxy, propoxy, isopropoxy or butoxy.

"Halogen" can signify Cl, Br, F or I.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like.

Those compounds in which R^4 signifies hydrogen, R^5 signifies methyl and n signifies 1 are preferred. Thereunder there fall those compounds in which R^1 signifies hydrogen, hydroxy, halogen or methyl, R^2 signifies hydrogen or ethyl and R^3 signifies hydrogen, methyl or methoxy.

Some particularly preferred representatives of the class of substance defined by general formula I in the scope of the present invention are:

rac-trans-8-Ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a, 5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-2,9-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one;

rac-cis-7-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-7-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

(+)-trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a, 5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

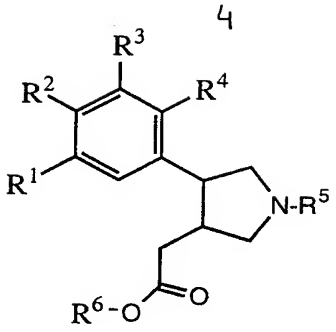
(+)-cis-2,7-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one;

(+)-cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and

(+)-cis-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one.

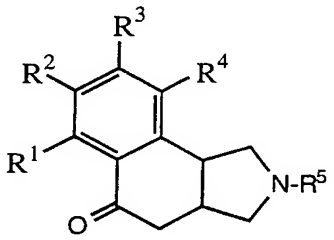
Compounds of general formula I as well as their pharmaceutically acceptable acid addition salts can be manufactured in according with the invention in a manner known per se by

a) cyclizing a compound of the general formula



II

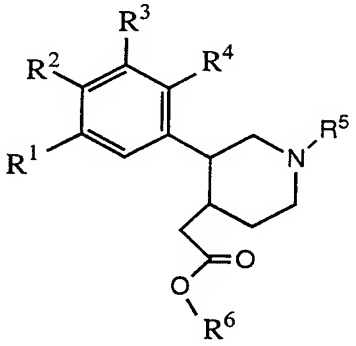
wherein R^6 signifies lower-alkyl,
to a compound of the general formula



IA

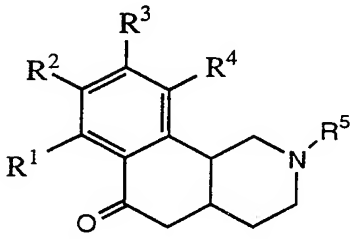
or

b) cyclizing a compound of the general formula



III

to a compound of the general formula



IB

or

c) alkylating or benzylating a compound of general formula I in which R^5 signifies hydrogen, or

d) desalkylating a compound of general formula I in which R^5 signifies alkyl or benzyl, or

e) in a compound of general formula I in which at least one of R^1-R^4 signifies an alkoxy group, converting this/these into (a) hydroxy group(s), and

f) if desired, converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salt.

In accordance with process variant a) the cyclization of a correspondingly substituted acetic acid ester of general formula II can be effected with polyphosphoric acid at a reaction temperature of about 120°C. Toluene is especially suitable as the solvent. Another cyclization method comprises the reaction of a corresponding ester with phosphorus oxychloride in the presence of a strong base.

The cyclization of a compound of formulae III to compounds of formulae IB (see Scheme 2) in accordance with variant b) is effected analogously to variant a). A mixture of polyphosphoric acid and toluene is reacted with a corresponding acetic acid ester for several hours at about 120°C and the product is subsequently purified according to known methods.

In accordance with process variant c) the alkylation or benzylation at the N atom of the ring nitrogen is effected with an alkyl or benzyl halide, preferably where methyl bromide, ethyl bromide, propyl bromide or benzyl bromide. Conveniently, a compound of general formula I in which R^5 signifies hydrogen is reacted with an aforementioned alkyl or benzyl halide in the

presence of an alkaline salt, for example K_2CO_3, in anhydrous DMF and about 125°C.

The desalkylation at the N atom of the ring nitrogen is effected in accordance with process variant d) by treating a compound of general formula I in which R^5 signifies alkyl in anhydrous chloroform and at room temperature with a cyanogen halide, preferably cyanogen bromide, subsequently heating under reflux and, after concentration under reduced pressure, again boiling under reflux with hydrochloric acid for several hours. Another possibility comprises treatment of a corresponding compound with 2,2,2-trichloroethyl chloroformate.

In accordance with process variant e) a compound of general formula I in which one of R^1-R^4 signifies an alkoxy group is converted into a compound of formula I in which one of R^1-R^4 signifies a hydroxy group. This is conveniently effected by converting the corresponding compound of formula I into the hydrochloride and subsequently converting the latter into the corresponding hydroxy compound at about -70°C using a BBr_3 solution in methylene chloride.

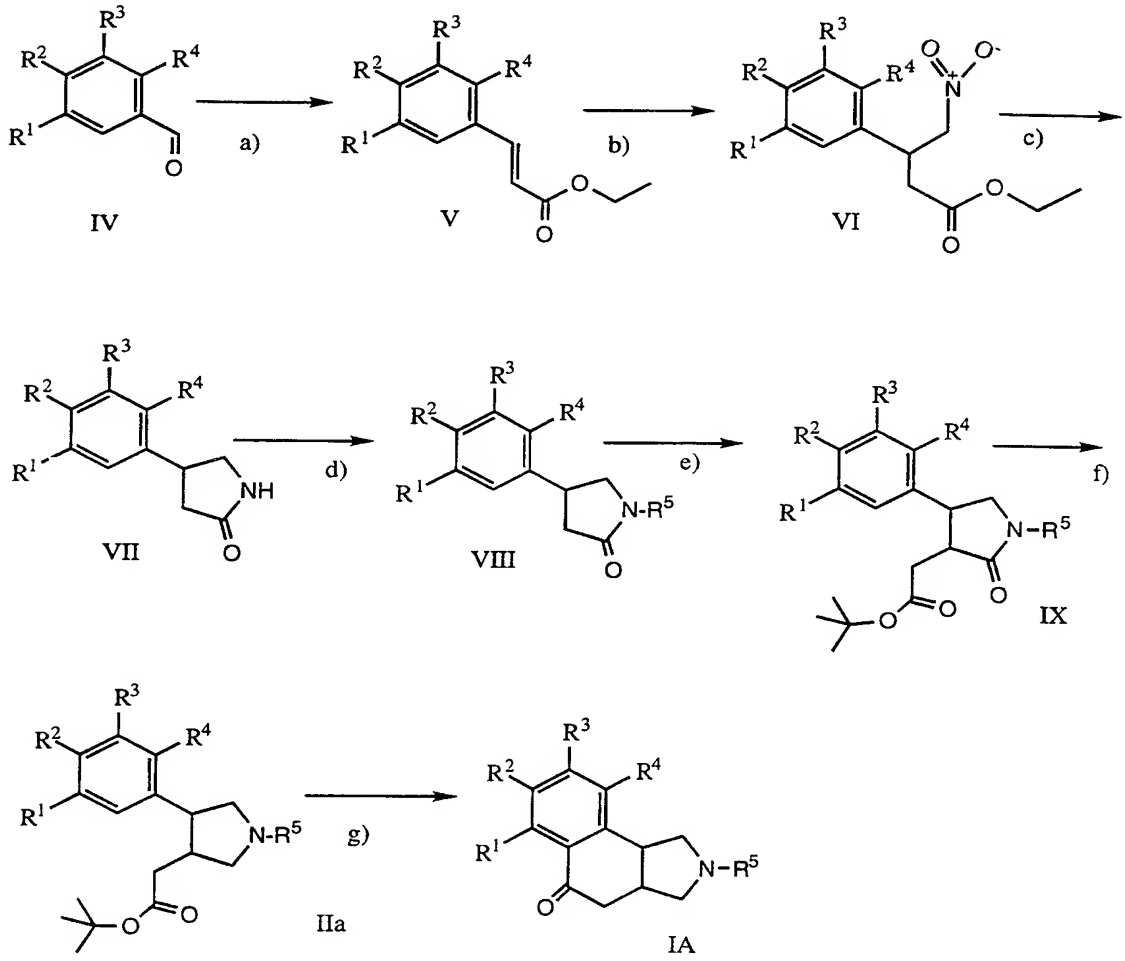
It has been found that for a pharmaceutical use of these compounds their acid addition salts are especially well suited. The addition of the corresponding acids to the compounds of formula I is conveniently effected prior to their final isolation at the conclusion of the described manufacturing variants.

The compounds required as precursors for the manufacture of the compounds of formula I can be prepared according to Schemes 1 and 2.

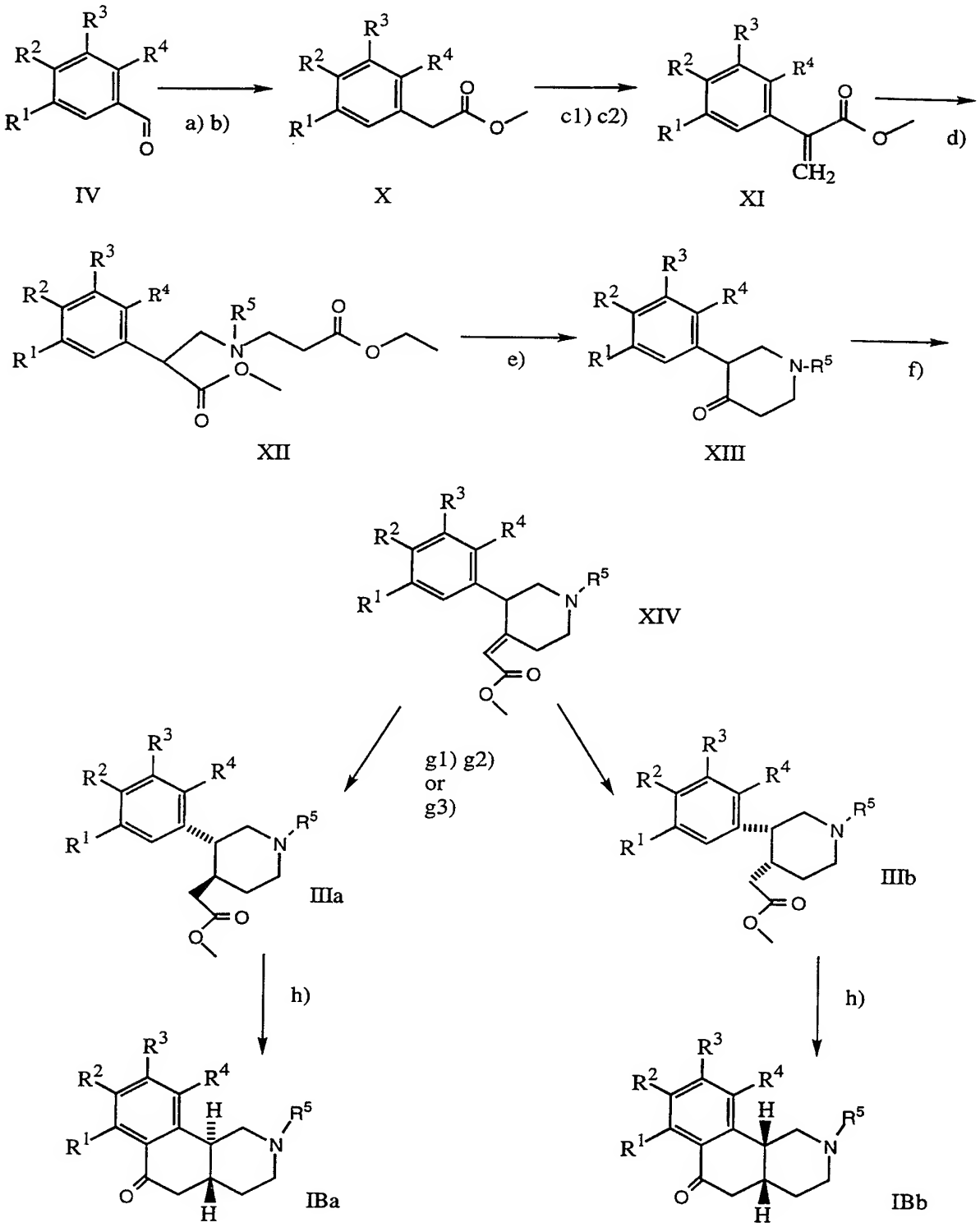
Scheme 1 describes the manufacture of the compounds of formula I in which n signifies 0. The steps for the synthesis are described in detail in Example 1a-1h as an example for the manufacture of cis-7-ethyl-6-hydroxy-8-methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one.

The manufacture of compounds of general formula I in which n signifies 1 is set forth in Formula Scheme 2. A detailed description for the manufacture of compounds of formulae IBa and IBb starting from a compound of general formula IV is described in Example 8a-8i as a concrete example for trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one.

Scheme 1 (according to Example 1)



Scheme 2 (according to Example 8)



The binding of compounds of formula I in accordance with the invention to the serotonin receptors was determined in vitro by standard methods. The compounds were investigated in accordance with the assays given hereinafter:

a) for the binding to the $5HT_{2C}$ receptor in accordance with the [3H]-5-HT binding assay according to the method of S.J. Peroutka et al., Brain Research 584, 191-196 (1992).

b) for the binding to the $5HT_{2A}$ receptor in accordance with the [3H]-DOB binding assay according to the method of T. Branchek et al., Molecular Pharmacology 38, 604-609 (1990).

The (p_{Ki} values $p_{Ki} = -\log_{10} Ki$) of the test compounds are given. The ki value is defined by the following formula:

$$Ki = \frac{IC_{50}}{1 + \frac{[L]}{K_D}}$$

in which the IC_{50} values are those concentrations of test compounds in nM by which 50% of the receptor-bound ligands are displaced. [L] is the concentration of ligand and the K_D value is the dissociation constant of the ligand.

The thus-determined activity of some compounds in accordance with the invention will be evident from the following Table:

Compound	Example	Test method	
		a $5HT_{2A}$	b $5HT_{2C}$
A	8	6.90	7.98
B	13	<5	7.22
C	15	5.17	7.26
D	17	6.2	7.86
E	31	<5	7.57
F	41	5.96	7.61
G	43	7.21	8.47
H	44	<5	7.00
I	46	<5	7.84
J	47	5.83	7.32
K	48	5.13	8.14

A = rac-trans-8-Ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

B = rac-7-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

C = rac-cis-2,9-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

D = rac-cis-7-Chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

E = rac-cis-7-Fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

F = rac-cis-2,7,9-Trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

G = (+)-trans-8-Ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinoline

H = (+)-cis-7-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

I = (+)-cis-2,7-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

J = (+)-cis-2,7,9-Trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

K = (+)-cis-2-Methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

The compounds of formula I and the pharmaceutically acceptable acid addition salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions, or nasally.

The compounds of formula I and the pharmaceutically acceptable acid addition salts of the compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oils and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable acid addition salt thereof and a therapeutically inert carrier are also an object of the present

invention, as is a process for their production which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of general formula I as well as their pharmaceutically acceptable acid addition salts can be used in the treatment or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive-compulsive disorders, social phobias or panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia etc.; nervous system damage caused by trauma, stroke, neurodegenerative diseases etc; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility and, respectively, for the production of corresponding medicaments. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In the case of oral administration the dosage lies in a range of about 0.01 mg to about 500 mg of a compound of general formula I or the corresponding amount of a pharmaceutically acceptable acid addition salt thereof, although the upper limit can also be exceeded when this is found to be indicated. The daily dosage can be administered as a single dosage or divided into several single dosages.

The following Examples illustrate the present example invention in more detail. However, they are not intended to limit its scope in any manner. All temperatures are given in degrees Celsius.

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Example 1

cis-7-Ethyl-6-hydroxy-8-methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one

a) 39.4 ml (63 mmol) of a 1.6N solution of n-butyllithium in hexane were added over a period of 15 minutes while stirring at -40° to a suspension of 28.3 g (66 mmmol) of ethoxycarbonylmethyl-triphenylphosphonium bromide in 200 ml of tetrahydrofuran. The reaction mixture was stirred at 0° for one hour, cooled to -70° and treated dropwise over 30 minutes with a solution of 11.6 g (60 mmol) of 4-ethyl-3,5-dimethoxy-benzaldehyde in 100 ml of tetrahydrofuran. Subsequently, the mixture was stirred at room temperature for a further 16 hours, poured into 600 ml of saturated sodium chloride solution and extracted twice with 800 ml of diethyl ether each time. The combined organic phases were washed once with 600 ml of saturated sodium chloride solution, dried ($MgSO_4$) and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 5:1). 12.5 g (79%) of ethyl 3-(4-ethyl-3,5-dimethoxy-phenyl)-acrylate were obtained as a white solid.

b) A mixture of 12.5 g (47.3 mmol) of ethyl (4-ethyl 3,5-dimethoxy-phenyl)-acrylate, 40 ml of nitromethane and 10 ml of a 40% solution of Triton B in methanol was stirred at 60° over 15 hours. Subsequently, the reaction mixture was poured on to 50 ml of ice and 50 ml of 3N sulphuric acid and extracted twice with 300 ml of ethyl acetate each time. The combined organic phases were washed twice with 100 ml of saturated sodium chloride solution each time, dried ($MgSO_4$) and concentrated in a vacuum. 15.1 g (98%) of ethyl 3-(4-ethyl-3,5-dimethoxy-phenyl)-4-nitro-butanoate were obtained as a yellow oil.

c) 15.1 g (46.4 mmol) of ethyl 3-(4-ethyl-3,5-dimethoxy-phenyl)-4-nitro-butanoate dissolved in 300 ml of ethanol were hydrogenated on Raney-nickel while stirring over a period of 2.5 hours. The catalyst was filtered off, washed several times

with ethanol and the combined ethanol phases were concentrated in a vacuum to a volume of 200 ml. The reaction mixture was treated with 1.7 g of sodium acetate and 50 mg of p-toluenesulphonic acid and heated under reflux over 24 hours. Subsequently, the mixture was concentrated in a vacuum and the residue was purified by column chromatography on silica gel (methylene chloride/methanol 19:1). 8.85 g (76%) of 4-(4-ethyl-3,5-dimethoxy-phenyl)-pyrrolidin-2-one were obtained as a beige solid with m.p. 156°.

d) 3.12 g (78 mmol) of a sodium hydride dispersion (60% in oil) were added using a spatula and while stirring to a suspension of 8.85 g (35.5 mmol) of 4-(4-ethyl-3,5-dimethoxy-phenyl)-pyrrolidin-2-one in 250 ml of tetrahydrofuran and 2 ml of dimethylformamide and the mixture was stirred at room temperature for a further hour. Thereafter, the reaction mixture was treated with 3.52 ml (106.5 mmol) of methyl iodide and left to stir at room temperature for a further 16 hours. Subsequently, the reaction mixture was poured on to 400 ml of ice-water and extracted twice with 600 ml of ethyl acetate each time. The combined organic phases were washed twice with 300 ml of saturated sodium chloride solution each time, dried ($MgSO_4$) and concentrated in a vacuum. The crude product was purified by column chromatography on silica gel (methylene chloride/methanol 39:1). 8.08 g (86%) of 4-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-pyrrolidin-2-one were obtained as a beige solid.

e) A solution of LDA in 20 ml of anhydrous tetrahydrofuran, freshly prepared at 0° from 1.35 ml (9.5 mmol) of diisopropylamine and 5.93 ml (9.5 mmol) of a 1.6N solution of n-butyllithium in hexane, was added dropwise while stirring to a solution, cooled to -70°, of 2 g (7.6 mmol) of 4-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-pyrrolidin-2-one in 20 ml of anhydrous tetrahydrofuran. The mixture was stirred at -70° for a further 30 minutes and subsequently a solution of 1.23 ml (8.35 mmol) of tert.-butyl bromoacetate in 20 ml of tetrahydrofuran was added dropwise thereto over 30 minutes. Thereafter, the mixture was stirred for a further 22 hours

without removal of the cooling bath, with the temperature slowly coming to room temperature. The mixture was poured on to 150 ml of ice-water and extracted twice 250 ml of ethyl acetate each time. The combined organic phases were washed once with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (ethyl acetate). In addition to 0.54 g of educt there were obtained 1.23 g (43% and, respectively, 58% based on the conversion) of tert-butyl-(4-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-2-oxo-pyrrolidin-3-yl)-acetate as a pale yellow oil.

f) A solution of 1.23 g (3 26 mmol) of tert.butyl (4-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-2-oxo-pyrrolidin-3-yl)-acetate in 20 ml of tetrahydrofuran was treated at room temperature while stirring with 32.6 ml (32.6 mmol) of a 1M borane-THF complex solution and subsequently heated under reflux for 7 hours. Thereafter the reaction mixture was cooled to 0°, 10 ml of methanol were slowly added dropwise thereto and the mixture was concentrated in a vacuum. The residue was purified by column chromatography on silica gel (ethyl acetate). 0.9 g (76%) of tert.-butyl 4-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-2-oxo-pyrrolidin-3-yl)-acetate was obtained as a colourless oil.

g) A mixture of 1.08 g (2.97 mmol) of tert.-butyl 4-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-2-oxo-pyrrolidin-3-yl)-acetate and 11 g of polyphosphoric acid was stirred at 120° over 75 minutes. The reaction mixture was subsequently adjusted to pH 6 with 28% NaOH and sodium acetate and extracted three times with 100 ml of methylene chloride each time. The combined organic phases were washed once with 50 ml of saturated sodium chloride solution, dried ($MgSO_4$) and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (methylene chloride/methanol/NH_4OH 15:1:0.1). 0.4 g (49%) of cis 7-ethyl-6-hydroxy-8-methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one was obtained as a colourless oil.

h) 168 mg (1.45 mmol) of fumaric acid and 50 ml of diethyl ether were added while stirring to a solution of 0.4 g (1.45 mmol) of cis-7-ethyl-6-hydroxy-8-methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one in 0.5 ml of ethanol. The mixture was stirred at room temperature for a further 17 hours and the solid was subsequently filtered off. 0.55 g (97%) of 7-ethyl-6-hydroxy-8-methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one fumarate (1:1) was obtained as a white solid with m.p. 195°.

Example 2

cis-7-Ethyl-6,8-dimethoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one

a) A mixture of 150 mg (0.41 mmol) of (4-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-pyrrolidin-3-yl)-acetate, 1.5 ml trifluoroacetic acid and 0.15 ml of trifluoroacetic acid anhydride was stirred at room temperature over 2 hours. The reaction mixture was subsequently poured on to 50 ml of ice-water, made basic with 28% NaOH and extracted twice with 100 ml of methylene chloride each time. The combined organic phases were washed once with 50 ml of saturated sodium chloride solution, dried ($MgSO_4$) and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (methylene chloride/methanol/NH_4OH 15:1:0.1). 15 mg (13%) of cis-7-ethyl-6,8-dimethoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one were obtained as a colourless oil.

b) 6 mg (0.05 mmol) of fumaric acid 10 ml of hexane and 10 ml of diethyl ether were added while stirring to a solution of 15 mg (0.05 mmol) of cis-7-ethyl-6,8-dimethoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one in 0.1 ml of ethanol. The mixture was stirred at room temperature for a further 2 hours and the solid was subsequently filtered off. 15 mg (75%) of cis-7-ethyl-6,8-dimethoxy-2-methyl-1,2,3,3a, 4,9b-hexahydro-benzo[e]isoindol-5-one fumarate (1:1) were obtained as a beige solid with m.p. 148°.

Example 3

cis-8-Methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]-isoindol-5-one

In an analogous manner to that described in Example 1 d)-h), from 4-(3-methoxy-phenyl)-pyrrolidin-2-one there was obtained cis-8-methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one fumarate (1:1) as a white solid with m.p. 193°.

Example 4

cis-2,8-Dimethyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one

In an analogous manner to that described in Example 1 b)-h), from ethyl 3-(3-methyl-phenyl)-acrylate there was obtained cis-2,8-dimethyl-1,2,3,3a,4,9b-hexahydro-benzo[e]-isoindol-5-one fumarate (1:1) as a white solid with m.p. 153°.

Example 5

cis-8-Chloro-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]-isoindol-5-one

In an analogous manner to that described in Example 1 b)-h), from ethyl 3-(3-chloro-phenyl)-acrylate there was obtained cis-8-chloro-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]-isoindol-5-one fumarate (1:0.5) as a white solid with m.p. 213°.

Example 6

cis-2-Methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one

In an analogous manner to that described in Example 1e)-h), from 1-methyl-4-phenyl-pyrrolidin-2-one there was

obtained cis-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]-isoindol-5-one fumarate (1:0.5) as a white solid with m.p. 203°.

Example 7

cis-7-Methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]-isoindol-5-one

In an analogous manner to that described in Example 1 e)-h), from 4-(4-methoxy-phenyl)-1-methyl-pyrrolidin-2-one there was obtained cis-7-methoxy-2-methyl-1,2,3,3a,4,9b-hexahydro-benzo[e]isoindol-5-one fumarate (1:1) as a white solid with m.p. 173°.

Example 8

trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2-H-benzo[h]isoquinoline-6-one

a) 130 ml of a 40% solution of benzyltrimethylammonium hydroxide in methanol (Triton B) were added to a solution of 126.5 g (651.2 mmol) of 4-ethyl-3,5-dimethoxy-benzaldehyde and 80.89 g (651.2 mmol) of methyl methylthiomethyl sulphoxide in 300 ml of tetrahydrofuran and the mixture was heated at reflux for 5 hours. After the addition of 300 ml of methylene chloride the mixture was extracted with 200 ml of 0.5M sulphuric acid. The organic phase was dried ($MgSO_4$), filtered and evaporated. Chromatography of the resulting residue (silica gel, ethyl acetate/hexane 1:1) yielded 134.6 g (69%) of (E)-2-ethyl-5-(2-methylsulphanyl-2-methyl-sulphinyl-vinyl)-1,3-dimethoxybenzene as a colourless oil, which gave colourless crystals of m.p. 82-83° by crystallization from hexane.

b) 400 ml of a concentrated methanolic hydrochloric acid solution were added to a solution of 130.0 g (433 mmol) of (E)-2-ethyl-5-(2-methylsulphanyl-2-methylsulphinyl-vinyl)-1,3-dimethoxybenzene in 200 ml of methanol and the mixture was stirred at 50° for 4 hours. Subsequently, the methanol was

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evaporated and the residue was partitioned between 300 ml of methylene chloride and 200 ml of sat. sodium hydrogen carbonate solution. The aqueous phase was washed twice with 200 ml of methylene chloride and the organic phases were dried ($MgSO_4$), filtered and evaporated. Chromatography of the residue (silica gel, ethyl acetate/hexane 1:9) yielded 100.5 g (94%) of methyl (4-ethyl-3,5-dimethoxy-phenyl)-acetate as a colourless wax, Rf = 0.345 (silica gel, ethyl acetate/hexane 1:9).

c 1) A solution of 80.43 g (337.5 mmol) of methyl (4-ethyl-3,5-dimethoxy-phenyl)-acetate in 400 ml of toluene was added dropwise to a suspension of 22.1 g (506 mmol) of NaH (55% in mineral oil) in 400 ml of tetrahydrofuran and 40.86 g (346 mmol) of dimethyl oxalate and the mixture was stirred at room temperature for 65 hours. The reaction mixture was poured on to 300 ml of ice-water and washed twice with 250 ml of diethyl ether. The aqueous phase was adjusted to pH 1 with 25% HCl and extracted three times with 300 ml of diethyl ether. The combined phases were dried ($MgSO_4$), filtered and evaporated. The thus-obtained dimethyl 2-(4-ethyl-3,5-dimethoxy-phenyl)-3-oxo-succinate (101.9 g, 314.3 mmol) was suspended in 150 ml of water and treated with 61 ml (812 mmol) of formaldehyde solution (37% in water). Subsequently, a solution of 43.4 g of potassium carbonate in 150 ml of water was slowly added dropwise thereto and the mixture was stirred at room temperature for 12 hours and then extracted three times with 250 ml of diethyl ether. The combined organic phases were dried ($MgSO_4$), filtered and evaporated. Chromatography of the resulting residue (silica gel, hexane/methylene chloride 1:2) gave 44.5 g (53%) of methyl 2-(4-ethyl-3,5-dimethoxy-phenyl)-acrylate as a colourless wax, Rf = 0.635 (silica gel, methylene chloride/hexane 2:1).

c 2) 18.9 g (630 mmol) of paraformaldehyde, 92.8 g (672 mmol) of potassium carbonate and 3.1 g (8.4 mmol) of tetrabutylammonium iodide were added to a solution of 100 g (420 mmol) of methyl 2-(4-ethyl-3,5-dimethoxy-phenyl)-acrylate in 200 ml of toluene and the mixture was heated to 80°

for 6 hours and then cooled and treated with 150 ml of water. The phases were separated and the aqueous phase was extracted twice with 120 ml of toluene. The combined organic phases were dried ($MgSO_4$), filtered and evaporated. Chromatography of the resulting residue (silica gel, hexane/methylene chloride 2:1) gave 70.5 g (67%) of methyl 2-(4-ethyl-3,5-dimethoxy-phenyl)-acrylate as a colourless wax, Rf = 0.635 (silica gel, methylene chloride/hexane 2:1).

d) A solution of 78.4 g (313 mmol) of methyl 2-(4-ethyl-3,5-dimethoxy-phenyl)-acrylate and 47.7g (364 mmol) of ethyl 3-methylamino-propionate was stirred at room temperature for 48 hours. Chromatography of the reaction mixture (silica gel, ethyl acetate/hexane 1:1) and crystallization from hexane gave 71.1 g (59%) of methyl 3-[(2-ethoxycarbonyl-ethyl)-methyl-amino]-2-(4-ethyl-3,5-dimethoxy-phenyl)-propionate as colourless crystals of m.p. 74-75°.

e) A solution of 53.51 g (140.3 mmol) of methyl 3-[(2-ethoxycarbonyl-ethyl)-methyl-amino]-2-(4-ethyl-3,5-dimethoxy-phenyl)-propionate in 150 ml of toluene was added dropwise at 80° to a suspension of 11.62 g (266.3 mmol) of sodium hydride (55% in mineral oil) in 150 ml of toluene and the mixture was subsequently heated at reflux for 15 hours. The solution was cooled to room temperature and adjusted to pH 1 with 6N hydrochloric acid. The toluene was separated and extracted once with 150 ml of 6N hydrochloric acid. The acidic phases were heated at reflux for 20 hours. After cooling to room temperature the mixture was adjusted to pH 14 with 28% NaOH and extracted three times with 250 ml of methylene chloride. The organic phases were washed once with 200 ml of water and once with 200 ml of saturated sodium chloride solution, dried ($MgSO_4$), filtered and evaporated. Chromatography (silica gel, methylene chloride/methanol 19:1) and recrystallization from hexane yielded 34.4 g (88%) of 3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-one as pale yellow crystals of m.p. 84-85°.

f) A solution of 39 ml (262.4 mmol) of trimethyl phosphonoacetate in 450 ml of tetrahydrofuran was added dropwise at 0° to a suspension of 9.54 g (238.5 mmol) of sodium hydride (55% in mineral oil) in 450 ml of tetrahydrofuran and the mixture was stirred for 30 minutes. Subsequently, the white suspension was treated with a solution of 33.15 g (119.5 mmol) of 3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-one in 450 ml of tetrahydrofuran and the mixture was stirred at 50° for 2 hours. After cooling to room temperature the mixture was poured on to 500 ml of ice-water and extracted three times with 400 ml of diethyl ether. The organic phases were washed with 400 ml of water and 400 ml of saturated sodium chloride solution, dried (Na_2SO_4), filtered and evaporated. Chromatography (silica gel, methylene chloride/methanol 19:1) and recrystalization from hexane yielded 36.33 g (91%) of methyl (E)-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-ylidene]acetate as pale yellow crystals of m.p. 110-112°.

g 1) 25.76 g (1060 mmol) of magnesium shavings were added to a solution of 35.33 g (106 mmol) of methyl (E)-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-ylidene]acetate in 850 ml of methanol and the mixture was stirred at room temperature for 2 hours. The solution was filtered over Dicalite and evaporated. The residue was partitioned between 300 ml of methylene chloride and 500 ml of saturated ammonium chloride solution. The aqueous phase was extracted three times with 250 ml of methylene chloride. The organic phase was dried (Na_2SO_4), filtered and evaporated. Chromatography (silica gel, ethyl acetate/methanol/NH_4OH 200:10:1) yielded 7.16 g (20%) of methyl cis-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-yl]-acetate as a colourless oil, Rf = 0.23 ((silica gel, ethyl acetate/methanol/ NH_4OH 200:10:1) and 23.51 g (66%) of methyl-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-yl]-acetate as a colourless oil, Rf = 0.12 (silica gel, ethyl acetate/methanol/NH_4OH 200:10:1).

g 2) A solution of 11.7 g (35.3 mmol) of methyl (E)-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-ylidene]acetate in

100 ml of methanol was treated with 500 mg of Pd on charcoal and hydrogenated with hydrogen at room temperature for 12 hours. The catalyst was filtered off and the filtrate was evaporated. Chromatography (silica gel, ethyl acetate/methanol/ NH_4OH 200:10:1) yielded 9.14 g (77%) of methyl cis-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-yl]-acetate as a colourless oil, Rf = 0.23 (silica gel ethyl acetate methanol/NH_4OH 200:10:1) and 2.56 g (21%) of methyl trans-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-yl]-acetate as a colourless oil, Rf = 0.12 (silica gel, ethyl acetate/methanol/NH_4OH 200:10:1).

g 3) A solution of 6.4 g (19.3 mmol) of methyl (E)-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-ylidene]acetate in 100 ml of methanol was treated with 1.08 g (20 mmol) of sodium methylate and the mixture was heated at reflux for 6 hours. The solution was evaporated and the residue was partitioned between 50 ml of methyl acetate and 50 ml of water. The organic phases were dried ($MgSO_4$), filtered and evaporated. The colourless oil was dissolved in 50 ml of methanol, treated with 125 mg of Pd on charcoal and hydrogenated with hydrogen at room temperature for 12 hours. The catalyst was filtered off and the filtrate was evaporated. Chromatography (silica gel, ethyl acetate/methanol/NH_4OH 200:10:1) yielded 5.68 g (88%) of methyl cis-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-yl]-acetate as a colourless oil, Rf = 0.23 (silica gel, ethyl acetate/methanol/NH_4OH 200:10:1).

h) A mixture of 140 g of polyphosphoric acid and 50 ml of toluene was heated to 120° and treated with a solution of 13.9 g (41.5 mmol) of methyl cis-[3-(4-ethyl-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-yl]-acetate in 120 ml of toluene. The reaction mixture was stirred at 120° for 3 hours and poured slowly into 500 ml of water at 80°. The mixture was adjusted to pH = 12 with 28% sodium hydroxide solution and extracted three times with 300 ml of ethyl acetate. The organic phase was dried (Na_2SO_4), filtered and evaporated. Chromatography (silica gel, methylene chloride/methanol/NH_4OH 110:10:1) gave 8.64 g (68%)

of trans-8-ethyl-7,9-dimethoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one as a colourless oil, Rf = 0.32 (silica gel, methylene chloride/methanol/NH_4OH 110:10:1), which was converted with fumaric acid into the fumarate (1:1) with m.p. 194-195.5°.

i) 3.9 (13 mmol) of trans-8-ethyl-7,9-dimethoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one were converted with HCl in ethyl acetate into the hydrochloride and the latter was subsequently dissolved in 280 ml of methylene chloride. The solution was cooled to -70° and treated with 15.4 ml of a 1M BBr_3 solution in methylene chloride. After 15 minutes the cooling bath was removed. After the solution had reached room temperature it was stirred for one hour, subsequently poured on to 200 ml of ice/sat. sodium hydrogen carbonate solution and extracted three times with 250 ml of methylene chloride. The organic phases were dried (Na_2SO_4), filtered and evaporated. Chromatography (silica gel, methylene chloride/methanol/NH_4OH 110:10:1) yielded 2.50 g (67%) of trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with fumaric acid into the fumarate (1:1) with m.p. 201-203°.

Example 9

cis-8-Ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 1 h) and i), from cis-8-ethyl-7,9-dimethoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one there was obtained cis-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with fumaric acid into the fumarate (1:1) with m.p. 221-223°.

Example 10

trans-8-Bromo-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

a) 2 ml of 1N NaOH solution were added to a solution of 0.726 g (1.87 mmol) of methyl trans-[3-(4-bromo-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-yl]-acetate in 3 ml of ethanol and the mixture was stirred at 50° for 30 minutes. The solution was evaporated and the residue was dried in a high vacuum. The thus-obtained sodium salt was suspended in 5 ml of acetonitrile. After the addition of 278 mg (2 mmol) of potassium carbonate the suspension was treated at 0° with 0.913 ml (10 mmol) of phosphorus oxychloride and the mixture was subsequently stirred at 50° for 2 hours. Subsequently, the mixture was poured into 10 ml of water, adjusted to pH = 12 with 28% NaOH and extracted three times with 15 ml of ethyl acetate. The organic phase was dried (Na_2SO_4), filtered and evaporated. Chromatography (silica gel, methylene chloride/methanol 95:5) yielded 0.385 g (58%) of trans-8-bromo-7,9-dimethoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. 226-228°.

b) A solution of 0.421 g (1:11 mmol) of trans-8-bromo-7,9-dimethoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h] isoquinolin-6-one hydrochloride in 40 ml of methylene chloride was treated at -70° with 1.23 ml of a 1M BBr_3 solution in methylene chloride. After 15 minutes the cooling bath was removed. After the solution had reached room temperature it was stirred for one hour, subsequently poured on to 80 ml of ice/sat. sodium hydrogen carbonate solution and extracted three times with 60 ml of methylene chloride. The organic phase was dried (Na_2SO_4), filtered and evaporated. Chromatography (silica gel, methylene chloride/methanol 9:1) yielded 0.315 g (83%) of trans-8-bromo-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-

one, which was converted with HCl in methanol into the hydrochloride with m.p. 257-259°.

The methyl [3-(4-bromo-3,5-dimethoxy-phenyl)-1-methyl-piperidin-4-yl]-acetate used was prepared from 4-bromo-3,5-dimethoxybenzaldehyde in an analogous manner to that described in Example 8a), b), c 1), d), e), f) and g 1).

Example 11

trans-7-Hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c1), d), e), f), g 1), h) and i), from methyl (3,5-dimethoxy-phenyl)-acetate there was obtained trans-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 12

cis-2-Methyl-1,3,4,4a,5,11b-hexahydro-2H-8,10-dioxa-2-aza-cyclopenta[b]phenanthren-6-one

In an analogous manner to that described in Example 10 a), from methyl cis-(3-benzo[1,3]dioxol-5-yl-1-methyl-piperidin-4-yl)-acetate there was obtained cis-2-methyl-1,3,4,4a,5,11b-hexahydro-2H-8,10-dioxa-2-aza-cyclopenta[b]-phenanthren-6-one, which was converted with fumaric acid into the fumarate (1:0.75) with m.p. > 250°.

The methyl cis-(3-benzo[1,3]dioxol-5-yl-1-methyl-piperidin-4-yl)-acetate used was prepared in an analogous manner to that described in Example 8 f) and g 3) from 3-benzo[1,3]dioxol-5-yl-1-methyl-piperidin-4-one.

Example 13

cis-9-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one and cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 f), g 3) and h), from 3-(3-methoxy-phenyl)-1-methyl-piperidin-4-one there were obtained cis-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one, which were converted with HCl in methanol into their hydrochlorides with m.p. > 250°.

Example 14

trans-9-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 f), g 1) and h), from 3-(3-methoxy-phenyl)-1-methyl-piperidin-4-one there was obtained trans-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 15

cis-2,9-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]iso-quinolin-6-one

In an analogous manner to that described in Example 8 d) e), f), g 3) and h), from methyl 2-m-tolyl-acrylate there was obtained cis-2,9-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

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Example 16

trans-2,9-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g1) and h), from methyl 2-m-tolyl acrylate there was obtained trans-2,9-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 17

cis-9-Chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one,
trans-9-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one,
cis-7-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and trans-7-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 1) and h), from methyl 2-(3-chloro-phenyl)-acrylate there were obtained cis-9-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, trans-9-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, cis-7-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and trans-7-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one which were converted with HCl in methanol into their hydrochlorides with m.p. > 250°.

Example 18

trans-8-Fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 1) and h), from methyl 2-(4-fluoro-phenyl)-acrylate there was obtained trans-8-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 19

cis-8-Fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 3) and h), from methyl 2-(4-fluoro-phenyl)-acrylate there was obtained cis-8-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 20

trans-2,8-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 1) and h), from methyl 2-o-tolyl-acrylate there was obtained trans-2,8-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

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Example 21

cis-2,8-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 3) and h), from methyl 2-o-tolyl-acrylate there was obtained cis-2,8-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 22

trans-8-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 f), g 1) and h), from 3-(4-methoxy-phenyl)-1-methyl-piperidin-4-one there was obtained trans-8-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. 222°.

Example 23

cis-8-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 f), g 3) and h), from 3-(4-methoxy-phenyl)-1-methyl-piperidin-4-one there was obtained cis-8-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 24

trans-8-Ethyl-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 1) and h), from methyl 2-(4-ethyl-phenyl)-acrylate there was obtained trans-8-ethyl-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. 226°.

Example 25

cis-8-Ethyl-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 3) and h), from 2-(4-ethyl-phenyl)-acrylic acid ester there was obtained cis-8-ethyl-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 26

trans-8-Chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one and cis-8-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 1) and h), from 2-(4-chloro-phenyl)-acrylic acid ester there were obtained trans-8-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and cis-8-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which were converted with HCl in methanol into their hydrochlorides with m.p. > 250°.

Example 27

cis-7,9-Difluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 3) and h), from methyl 3,5-difluorophenyl-acetate there was obtained cis-7,9-difluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 230°.

Example 28

trans-7,9-Difluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 1) and h), from methyl 3,5-difluorophenyl-acetate there was obtained trans-7,9-difluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 220°.

Example 29

cis-7,9-Dichloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and trans-7,9-dichloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 1) and h), from ethyl 3,5-dichlorophenyl-acetate there were obtained cis-7,9-dichloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and trans-7,9-dichloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which were converted with HCl in methanol into their hydrochlorides with m.p. > 250°.

Example 30

trans-9-Fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and trans-7-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 1) and h), from ethyl 3-fluorophenylacetate there were obtained trans-9-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and trans-7-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which were converted with HCl in methanol into their hydrochlorides with m.p. > 250°.

Example 31

cis-9-Fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one and cis-7-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 3) and h), from ethyl 3-fluorophenyl acetate there were obtained cis-9-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and cis-7-fluoro-2-methyl-1,3,4,4a, 5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which were converted with HCl in methanol into their hydrochlorides with m.p. > 250°.

Example 32

cis-2-Methyl-8-phenyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 3) and h), from methyl (4-phenyl)-phenyl acetate there was obtained cis-2-methyl-8-phenyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which

was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 33

trans-2-Methyl-8-phenyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 1) and h), from methyl (4-phenyl)-phenyl acetate there was obtained trans-2-methyl-8-phenyl-1,3,4, 4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 34

cis-8,9-Difluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 3) and h), from methyl 3,4-difluorophenyl-acetate there was obtained cis-8,9-difluoro-2-methyl-1,3,4, 4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 35

trans-8,9-Difluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 1) and h), from methyl 3,3-difluoro-phenyl acetate there was obtained trans-8,9-difluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 36

cis-10-Fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 f), g 3) and h), from 3-(2-fluorophenyl)-1-methyl-piperidone there was obtained cis-10-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 220°.

Example 37

trans-10-Fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 f), g 1) and h), from 3-(2-fluorphenyl)-1-methyl-piperidone there was obtained trans-10-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 220°.

Example 38

cis-10-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and trans-10-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 2) and h), from methyl 2-(2-methoxy-phenyl)-acrylate there were obtained cis-10-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and trans-10-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one, which were converted with HCl in methanol into their hydrochlorides with m.p. > 220°.

Example 39

cis-2,10-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 3) and h), from methyl 2-(2-methyl-phenyl)-acrylate there was obtained cis-2,10-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 220°.

Example 40

trans-2,10-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 8 d), e), f), g 1) and h), from methyl 2-(2-methyl-phenyl)-acrylate there was obtained trans-2,10-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 220°.

Example 41

trans-2,7,9-Trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 3) and h), from methyl (3,5-dimethyl-phenyl)-acetate there was obtained trans-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 42

cis-2,7,9-Trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 8 c 2), d), e), f), g 1) and h), from methyl (3,5-dimethyl-phenyl)-acetate there was obtained cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride with m.p. > 250°.

Example 43

(-)-trans-8-Ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

3.08 g (8.6 mmol) of (+) -O,O-dibenzoyltartaric acid were added to a solution of 2.58 g (8.6 mmol) of trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one in 40 ml of ethanol and the mixture was stirred at room temperature for 15 minutes. Subsequently, it was heated to reflux and sufficient ethanol was added thereto in order to give a clear solution (about 80 ml). After cooling to room temperature the resulting crystals (2.52 g) were filtered off and dissolved in a mixture of 50 ml of methylene chloride and 50 ml of 2N sodium carbonate solution. The sodium carbonate solution was washed once with methylene chloride. The organic phases were dried ($MgSO_4$), filtered and evaporated. The yellow oil obtained (1.18 g) was converted with HCl in methanol into the hydrochloride. After recrystallization from diisopropyl ether/ethanol there was obtained 0.86 g of (+)-trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one hydrochloride with m.p. 261-263, $[\alpha]_{589}$ = +28.6 (c = 0.5, H_2O).

The mother liquor of the crystallization with (+) -O,O-dibenzoyltartaric acid was evaporated and the residue was partitioned between methylene chloride and a 2N sodium

carbonate solution. The aqueous phase was washed twice with methylene chloride and the organic phases were dried ($MgSO_4$), filtered and evaporated. The thus-obtained light yellow oil (1.39 g (4.8 mmol)) was dissolved in 20 ml of ethanol and treated with 1.72 g (4.8 mmol) of (-)-O,O'-dibenzoyltartaric acid. Subsequently, the mixture was heated to reflux and sufficient ethanol was added thereto to give a clear solution (about 40 ml). After cooling to room temperature the resulting crystals (2.26 g) were filtered off and dissolved in a mixture of 50 ml of methylene chloride and50 ml of 2N sodium carbonate solution. The sodium carbonate solution was washed once with methylene chloride. The organic phases were dried ($MgSO_4$), filtered and evaporated. The thus-obtained yellow oil (1.22 g) was converted with HCl in methanol into the hydrochloride. After recrystallization from diisopropyl ether/ethanol there was obtained 0.82 g of (-)-trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one hydrochloride with m.p. 261-263°, $[\alpha]_{589}$ = -29.2 (c = 0.5, H_2O).

Example 44

(+)-cis-7-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

(-)-cis-7-Methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 43, from cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one by crystallization with (+)-O,O-dibenzoyltartaric acid there was obtained (+)-cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride. After recrystallization from ethanol there was obtained (+)-cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one hydrochloride with m.p. >250°, $[\alpha]_{589}$ = +2.6 (c = 0.5, H_2O).

By crystallization with (-)-O,O-dibenzoyltartaric acid there was obtained (-)-cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride. After recrystallization from ethanol there was obtained (-)-cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one hydrochloride with m.p. > 250°, $[\alpha]_{589}$ = -2.4 (c = 0.5, H_2O).

Example 45

(-)-trans-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 43, from trans-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one by crystallization with (+)-O,O'-dibenzoyltartaric acid there was obtained (+)-trans-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride. After recrystallization from ethanol there was obtained (+)-trans-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one hydrochloride with m.p. > 250, $[\alpha]_{589}$ = +39.5 (c = 0.5, methanol).

By crystallization with (-)-O,O'-dibenzoyltartaric acid there was obtained (-)-cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with HCl in methanol into the hydrochloride. After recrystallization from ethanol there was obtained (-)-trans-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one hydrochloride with m.p. > 250°, $[\alpha]_{589}$ = -41.2 (c = 0.5, methanol).

Example 46

(+)-cis-2,7-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

(-)-cis-2,7-Dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 43, from cis-2,7-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one by crystallization with (+)-O,O-dibenzoyl-tartaric acid there was obtained (+)-cis-2,7-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with fumaric acid in ethanol into the fumarate. After recrystallization from ethanol there was obtained (+)-cis-2,7-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one fumarate (1:1) with m.p. 230.5-232°, $[\alpha]_{589}$ = +6.8 (c = 0.5, H_2O).

By crystallization with (-)-O,O-dibenzoyltartaric acid there was obtained (-)-cis-2,7-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with fumaric acid in ethanol into the fumarate. After recrystallization from ethanol there was obtained (-)-cis-2,7-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one fumarate (1:1) with m.p. 230.5-232°, $[\alpha]_{589}$ = -5.6 (c = 0.5, H_2O).

Example 47

(+)-cis-2,7,9-Trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one

(-)-cis-2,7,7-Trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one

In an analogous manner to that described in Example 43, from cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo-[h]isoquinolin-6-one by crystallization with (+)-O,O'-dibenzoyl-tartaric acid there was obtained (+)-cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was

converted with fumaric acid in ethanol into the fumarate. After recrystallization from ethanol there was obtained (+)-cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one fumarate (1:1) with m.p. 219-220°, $[\alpha]_{589}$ = +22.8 (c = 0.5, H_2O).

By crystallization with (-)-O,O-dibenzoyltartaric acid there was obtained (-)-cis-2,7,7-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with fumaric acid in ethanol into the fumarate. After recrystallization from ethanol there was obtained (-)-cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one fumarate (1:1) with m.p. 219-220°, $[\alpha]_{589}$ = -22.8 (c = 0.5, H_2O).

Example 48

(-)-cis-2-Methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

(+)-cis -2-Methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 43, from cis-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one by crystallization with (-)-O,O'-di-p-toluoyltartaric acid there was obtained (-)-cis-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with fumaric acid in ethanol into the fumarate. After recrystallization from ethanol there was obtained (-)-cis-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one fumarate (1:1) with m.p. 206.5-208.5°, $[\alpha]_{589}$ = -21.6 (c = 0.5, H_2O).

By crystallization with (+)-O,O'-di-p-toluoyltartaric acid there was obtained (+)-cis-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with fumaric acid in ethanol into the fumarate. After recrystallization from ethanol there was obtained (+)-cis-2-methyl-

1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one fumarate (1:1) with m.p. 207-209°, $[\alpha]_{589}$ = + 20.8 (c = 0.5, H_2O).

Example 49

cis-8-Fluoro-2-propyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

a) 0.45 g (1.92 mmol) of 8-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one was dissolved in 6 ml of anhydrous chloroform and added dropwise at room temperature over 15 minutes to a solution of 244 mg (2.3 mmol) of cyanogen bromide in 2 ml of anhydrous chloroform. Subsequently, the mixture was heated under reflux for a further 75 minutes, concentrated in a vacuum, taken up with 12 ml of 2N hydrochloric acid and heated under reflux over 6 hours. Subsequently, the mixture was made basic with 3N sodium hydroxide solution and extracted three times with 50 ml of diethyl ether each time. The combined organic phases were washed once with 70 ml of saturated sodium chloride solution, dried ($MgSO_4$) and concentrated in a vacuum. 0.29 g (69%) of cis-8-fluoro-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one was obtained as a yellow oil.

b) A mixture of 0.29 g (1.32 mmol) of cis-8-fluoro-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, 0.12 ml (1.39 mmol) of bromopropane, 0.2 g (1.45 mmol) of potassium carbonate and 20 ml of anhydrous DMF was heated to 125°C for 1 hour. Subsequently, the mixture was poured into 3 ml of water and extracted once with 50 ml of ethyl acetate. The organic phase was washed once with 40 ml of saturated sodium chloride solution, dried ($MgSO_4$) and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (methylene chloride/methanol/NH_4OH 9:1:0.2). There were obtained 220 mg (63%) of cis-8-fluoro-2-propyl-1,3,4,4a, 5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

as a yellow oil, which was converted with MeOH/HCl into the hydrochloride with m.p.>220°.

Example 50

cis-8-Fluoro-2-ethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 49 b), from cis-8-fluoro-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one by alkylation with ethyl bromide there was obtained cis-8-fluoro-2-ethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with MeOH/HCl into the hydrochloride with m.p. > 220°.

Example 51

cis-2-Benzyl-8-fluoro-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one

In an analogous manner to that described in Example 49 b), from cis-8-fluoro-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one by alkylation with benzyl bromide there was obtained cis-2-benzyl-8-fluoro-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted with MeOH/HCl into the hydrochloride with m.p. > 220°.

Example 52

(+)-7,9-Dimethyl-2-propyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one

In an analogous manner to that described in Example 49 b), from (+)-7,9-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one by alkylation with bromopropane there was obtained (+)-7,9-dimethyl-2-propyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one, which was converted

with fumaric acid into the fumarate (1:1) with m.p. 220.5-226.5°, $[\alpha]_{589}$ = +33.7 (c = 0.5, H_2O).

The (+)-7,9-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one used was prepared as follows:

a 2.1) 0.76 ml (5.65 mmol) of 2,2,2-trichloroethyl chloroformate was added at 100° to a suspension of 500 mg (2.26 mmol) of (+)-cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and 120 mg of K_2CO_3 in 20 ml of toluene and the mixture was heated at reflux for 16 hours. Subsequently, the solution was cooled to room temperature and poured on to 40 ml of ice-water. The aqueous phase was extracted twice with 50 ml of ethyl acetate, dried ($MgSO_4$), filtered and evaporated. Chromatography of the residue (silica gel, hexane/ethyl acetate 4:1) yielded 890 mg (97%) of 2,2,2-trichloroethyl 7,9-dimethyl-6-oxo-3,4,4a,5,6,10b-hexahydro-1H-benzo[h]isoquinoline-2-carboxylate as a colourless oil.

a 2.2) 250 mg of Zn powder were added to a solution of 890 mg (2.2 mmol) of 2,2,2-trichloroethyl 7,9-dimethyl-6-oxo-3,4,4a,5, 6,10b-hexahydro-1H-benzo[h]-isoquinoline-2-carboxylate in 10 ml of glacial acetic acid and the mixture was stirred at room temperature for 16 hrs. The solution was filtered and adjusted to pH 10 with 28% NaOH. The aqueous phase was extracted twice with the 30 ml of methylene chloride, dried (Na_2SO_4), filtered and evaporated. Chromatography of the residue (silica gel, methylene chloride/methanol/NH_4OH 200:10:1) yielded 420 mg (83%) of 7,9-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one as a colourless oil.

Example A

Tablets of the following composition are produced in the usual manner:

	mg/tablet
Active ingredient	100
Powd. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in the usual manner:

	mg/tablet
Active ingredient	200
Powd. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

Capsules of the following composition are produced:

	mg/capsule
Active ingredient	50
Cryst. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active substance having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

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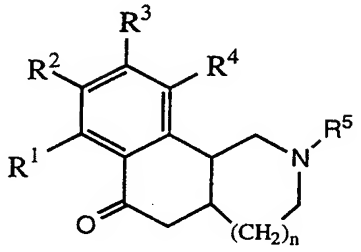
Claims

1. Compounds of the general formula



I

wherein

R^1-R^4 each independently signify hydrogen, halogen, hydroxy, lower alkyl, lower-alkoxy or phenyl or R^2 and R^3 together represent -O-CH_2-O-;

R^5 signifies hydrogen, lower-alkyl or benzyl; and

n signifies 0 or 1,

as well as pharmaceutically acceptable acid addition salts of the compounds of formula I, with the exception of racemic 2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinoline-6-one.

2. Compounds of general formula I according to claim 1 wherein R^4 signifies hydrogen, R^5 signifies methyl and n signifies 1.

3. Compounds according to claim 2, wherein R^1 signifies hydrogen, hydroxy, halogen or methyl, R^2 signifies hydrogen or ethyl and R^3 signifies hydrogen, methyl or methoxy.

4. Compounds according to claims 1-3,

rac-trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-7-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-2,9-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-7-chloro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-7-fluoro-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

rac-cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

(+)-trans-8-ethyl-7-hydroxy-9-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinoline;

(+)-cis-8-methoxy-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

(+)-cis-2,7-dimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one;

(+)-cis-2,7,9-trimethyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and

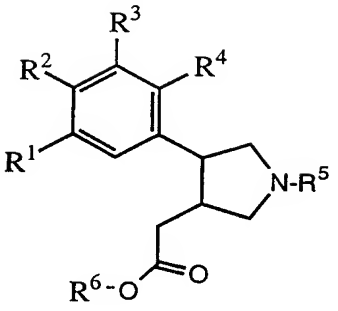
(+)-cis-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]-isoquinolin-6-one.

5. A medicament containing a compound according to any one of claims 1-4 and a therapeutically inert carrier material.

6. A medicament based on a compound I according to claim 1 and its pharmaceutically acceptable acid addition salts for the treatment or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive-compulsive disorders, social phobias or panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia, etc., nervous system damage caused by trauma, stroke, neuro-degenerative diseases etc.; cardiovascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

7. A process for the manufacture of compounds according to any one of claims 1-4, which process comprises

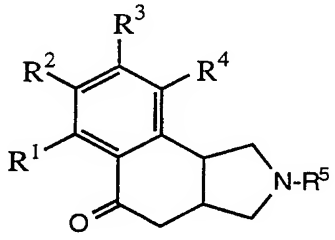
a) cyclizing a compound of the general formula



II

wherein R^6 signifies lower-alkyl,

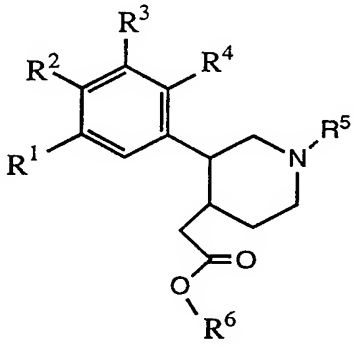
to give a compound of the general formula



IA

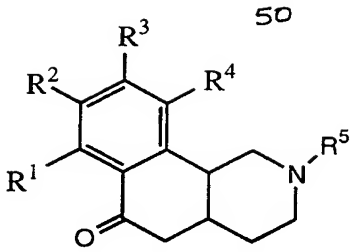
wherein the substituents R^1-R^5 have the significances set forth in claim 1, or

b) cyclizing a compound of the general formula



III

to give a compound of the general formula



IB

wherein R^1-R^5 have the significance set forth in claim 1 and R^6 has the significance given earlier in this claim,

or

c) alkylating or benzylating a compound of general formula I in which R^5 signifies hydrogen, or

d) desalkylating a compound of general formula I in which R^5 signifies alkyl or benzyl, or

e) in a compound of general formula I in which at least one of R^1-R^4 signifies an alkoxy group, converting this/these into (a) hydroxy group(s), and

f) if desired, converting the compound of formula I obtained into a pharmaceutically acceptable acid addition salt.

8. Compounds according to any one of claims 1-4, insofar as they are manufactured according to the process defined in claim 7 or a process equivalent thereto.

9. Compounds according to any one of claims 1-4, as well as pharmaceutically acceptable salts thereof for use as therapeutically active substances.

10. The use of compounds according to any one of claims1-4 and of rac.-2-methyl-1,3,4,4a,5,10b-hexahydro-2H-benzo[h]isoquinolin-6-one and of pharmaceutically usable salts thereof, especially for the treatment or prevention of central nervous disorders such as depressions, bipolar disorders, anxiety states, sleep and sexual disorders, psychoses, schizophrenia,

migraine and other conditions associated with cephalic pain or pain of a different kind, personality disorders or obsessive-compulsive disorders, social phobias or panic states, mental organic disorders, mental disorders in childhood, aggressivity, age-related memory disorders and behavioural disorders, addiction, obesity, bulimia, etc., nervous system damage caused by trauma, stroke, neurodegenerative diseases etc.; cardio-vascular disorders such as hypertension, thrombosis, stroke etc.; and gastrointestinal disorders such as dysfunction of the gastro-intestinal tract motility, and, respectively, for the production of corresponding medicaments.

11. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

Inte .ional Application No
PCT/EP 98/00043

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D221/10 C07D209/62 A61K31/435 A61K31/40 C07D491/04
//(C07D491/04,317:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and. where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 19 26 022 A (SANDOZ AG) 4 December 1969 cited in the application see claims and examples 1 and 2	1-3,5,6, 10
A	EP 0 461 353 A (ABBOTT LABORATORIES) 18 December 1991 see claims	1-10
A	EP 0 201 085 A (PENNWALT CORPORATION) 12 November 1986 see claims	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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1

Date of the actual completion of the international search	Date of mailing of the international search report
21 April 1998	28/04/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Henry, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .ional Application No
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